

NO DRAWINGS

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Date of Application and filing Complete Specification: June 1, 1966. No. 24375/66.

Application made in United States of America (No. 494,894) on Oct. 11, 1965. Complete Specification Published: Jan. 17, 1968.

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Index at acceptance:—C2 C(1Q4, 1Q6C, 1Q7A, 1Q8A, 1Q8B, 1Q8C, 1Q8D, 1Q9B, 1Q9L, 1Q11G); A5 E(1A4B2, 1A4B3, 1A4B4, 2); A5 R(83H, 83K); C5 D(6B4, 6B8, 6B10C, 6B12A, 6B12B1, 6B12B2, 6E12E, 6B12K2, 6B12M); D2 B13X

Int. Cl.:—C 07 d 87/02, C 07 d 93/08, C 07 d 95/00

COMPLETE SPECIFICATION

Benzoazinediones and Germicidal Compositions made therewith

We, STECKER INTERNATIONAL S.P.A., a body corporate organised under the laws of Italy, of Via Turati No. 29, Milan, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the preparation of new benzoazinediones, including benzothioxazinediones and benzoxazinediones, and to novel germicidal compositions prepared therewith. The compounds which are the subject of the present invention fall within the generic formula:

where X and X¹ are chlorine, bromine, iodine or CF₂,
n is an integer from 0 to 3, subject to the proviso that X or X¹ represent at

least one and not more than two CF, groups,

Y is sulphur or oxygen, and Z is sulphur or carbon.

The small numerals within the nuclei are inserted merely for more convenient orientation of the derivatives to be discussed herein.

The compounds of the present invention may be prepared by reacting a substituted salicylanilide with thionyl chloride, phosgene, or ethyl chloroformate according to the following typical reactions:

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In reaction (1) 3,5-dibromo-3'-(trifluoromethyl) salicylanilide is reacted with thionyl chloride to produce 6,8-dibromo-3-(3-trifluoromethylphenyl)-1,3-benzothiox-azine-2,4-dione. In reaction (2) the same salicylanilide is reacted with ethyl chloroformate to produce 6,8-dibromo-3-(3-trifluoromethylphenyl)-1,3-benzoxizine-2,4-dione.

These compounds may be prepared according to the method described by Stanseth, Baker and Roman, J. Med. Chem., 6, 1212 (1963). A typical method of preparation is as follows:

is as follows:

6,8-Dibromo-3-(3-trifluoromethylphenyl)-1,3-benzoxaxine-2,4-dione.

A molal solution of 3,5-dibromo-3'-(trifluoromethyl) salicylanilide in a mixture of pyridine and acetonitrile is stirred at 2—5°C, during dropwise addition of a molal quantity of ethyl chloroformate. Stirring is continued for 1—2 hours while the temperature is gradually increased to 120°—125°C. After about 60 mls. of distillate has been collected in a Barrett trap, the mixture is slowly cooled and, before it is solidified, water and concentrated HCl are added with stirring and further cooling. The crude product is then isolated, washed with water, and air-dried. The compound may be recrystallized from acetone, after decolorization with activated charcoal. The recrystallized product is then recovered.

Table I gives a list of compounds which have been prepared in accordance with

the foregoing method.

Š	Salicylanilide	Resciant	Product	Properties
l	3,5-Dibromo-3'-(trifluoromethyl)	so cr.	6,8-dibromo-3-(3-trifluoromethyl- phenyl)-1,3-benzothioxazine-2,4-dione	m.p. 190—5°C.
	3,5-Dibromo-3'-(trifluoromethyl)	Bthyl chloroformate	6,8-dibromo-3-(3-trifluoromethyl- pbenyl)-1,3-benzozzzno-2,4-dione	нр. 233—5°С.
	3'-(trifluoromethyl)	Ethyl chloroformate	3-(3-trifluoromethylphenyl)-1,3- benzoxzzinc-2,4-dione	m.p. 198—199°C.
	2'-Chloro-3'-(trifluoromethyl)	Ethyl chloroformate	3-(2-chloro-3-trifluoromethylphenyl)- 1,3-benzoxazine-2,4-dime	щр. 195—198°С.
•	3,5-Diodo-3',5'-bis(trifluoromethyl)	Ethyl chloroformste	6,8-diiodo-3-(3,5-bis(trifluoromethyl- phenyl)-1,3-benzozazine-2,4-dione	m.p. 214—8°C.
	2-Thiopbenyl-3,5-dibromo-3'- (triffuoromethyl)	Ethyl chloroformate	6,8-dibromo-3-(3-trifluoromethyl- phenyl)-1,3-benzothiazine-2,4-dione	m.p. 238—40°C.
	3,5-Dichloro-4-(trifluoromethyl)- 4'-jodo	Khyl chloroformate	6,8-dichloro-7-(trifluoromethyl)-3 (4-lodophenyl)-1,3-benzoxazine- 2,4-dione	н. 20 20

	The compounds of the present invention have been found to show unexpectedly	
•	The compounds of the present invention have confident to similar growths, as high toxicity to micro-organisms, such as bacteria, fungi, and similar growths, as high toxicity to micro-organisms, such as because known compounds. The antibacterial	
	high toxicity to micro-organisms, such as bacteria, rungi, antibacterial compared to the unsubstituted or heretofore known compounds. The antibacterial compared to the unsubstituted or heretofore known in Table II, as the minimum inhibitory	
	compared to the unsubstituted or herecorde known compounds activity of the present compounds is shown in Table II, as the minimum inhibitory activity of the present compounds is shown in Table II, as the minimum inhibitory activity of the present compounds in the present compounds at 24-hour broth culture of each	_
_	activity of the present compounds is shown in Table II, as the influence of each concentration (MIC), against Staphylococus aureus. A 24-hour broth culture of each concentration (MIC), against Staphylococus aureus.	5
5	concentration (MIC), against outphysican (BHI) broth.	
	organism was made in Brain Heart Infusion (BHI) broth. organism was made in Brain Heart Infusion (BHI) broth, were A number of screw cap test mbes, each containing 9 mls. of BHI broth, were	
	A number of screw cap lest moss, take at 1709C. A number of 100 ml.	
	propared and sternized for 15 initiates at 2 PUI book also were prepared, were	
	volumetric flasks, each commaning about the the same manner as were the test tubes.	10
- 10	capped with glass caps, and were statuted to be sorted upon accurately weighed and	
	One tenth of a gram of the compound that the same transferred with asentic	
	was dissolved in acctone or alcohol. The mixture flesh accompany the RHT broth.	
	was dissolved in acctone or alcohol. The mixture then was transferred to the previously sterilized volumetric flasks containing the BHI broth. technique to the previously sterilized volumetric flasks containing the BHI broth. This	
	technique to the previously sterilized volumetric mass command to the previously sterilized volumetric mass command to mix BHI broth. This With aseptic technique, the mixture was brought up to 100 ml. with BHI broth. This	15
15	With aseptic technique, the mixture was together was together then consisted of 1:1000 dilution of the compound to be tested. mixture then consisted of 1:1000 dilution of the compound to be tested.	
15	mixture then consisted of 1:1000 dilution of the compound to be sterile capped tube by Ten ml. of this mixture were transfered assertically to a sterile capped tube by	
	Ten ml. of this mixture were transfered assphicately to a mixture with a 10 ml. Mohr pipette. Scraid dilutions then were made from this stock solution with a 10 ml. Mohr pipette. Scraid dilutions then were made from this stock solution with a 10 ml. Mohr pipette. Scraid dilutions then were made from this stock solution with	
	a 10 ml. Mohr pipette. Serial dilutions then were made from this stock of the com- concentrations of 1:10,000, 1:100,000, 1:1,000,000 and 1:1,100,000,000 of the com-	
	concentrations of 1. 10,000,	20
	pounds. To each of the dilutions of a given compound then were added 0.1 ml. of a 24-	20
20	To each of the dilutions of a given compound that water at the broth solutions hour broth culture of the organism to be tested. The urbidity of the broth solutions hour broth culture of the organism to be tested. The density of the broth solutions are visible to the density of the broth solutions.	
	hour broth culture of the organism to be tested. The throadly of the over visible was determined by a Welsh Densichron. The densitometer was chosen over visible was determined by a Welsh Densichron, when end points were questionable. The broth	-
	was determined by a Welsh Densichron. The densitative were questionable. The broth observation for purposes of accuracy when end points were questionable. The broth observation for purposes of accuracy when end points were questionable. The broth observation for purposes of accuracy when end for 24 hr, at 37°C. A control consisting of 0.1 ml.	
	observation for purposes of accuracy when end points were distributed to stand for 24 hr. at 37°C. A control consisting of 0.1 ml. dilutions were then allowed to stand for 24 hr. at 37°C. A control consisting of 0.1 ml.	
	dilutions were then allowed to stand for 24 hr. at 57°C. A change of a 24-hour broth culture and 9 ml. of BHI broth also was prepared and was of a 24-hour broth culture and 9 ml. of grangeneds to be tested. At the end of the	25
25	of a 24-hour broth culture and a line to be tested at the end of the	
	subjected to the same conditions as in absented with the densitometer. If growth	
	24-hour period, the tubes again were disting in the booth	
	24-hour period, the tubes again were used to the same testing and their antibacterial activities	
	All compounds were subcetted to the same of the same o	30
30	were compared.	
	The unsubstituted compound No. 1 of Table 2 was nation. The expression ineffectiveness, as compared to the compounds of the present invention. The expression ineffectiveness, as compared to the compounds of the present invention. The expression ineffectiveness, as compared to the compounds of the present invention.	
	ineffectiveness, as compared to the compounds of the filling action against	
	"germicidal or annoacterial activity meaning of the present invention have	
	bactera fungi and similar organisms. The Cambi R coli I conei and others.	35
35	been found effective against organisms some compressing one or more com-	•-
33	The present germicides are useful in compositions comparing the present invention and a germicidally inert material, i.e., relatively pounds of the present invention and a germicidally inert material, i.e., relatively pounds of the present invention and a germicidally inert soap and/or detergent, and plastics	
	pounds of the present invention and a germicularly and the determine and plastics	
	pounds of the present invention and a germicutary little and of detergent, and plastics speaking, such as an inert pharmaceutical diluent, soap and/or detergent, and plastics speaking, such as an inert pharmaceutical diluent, soap and/or detergent, and plastics	
	speaking, such as an inert pharmaceutical dittem, stap and/or cubber. Fibrous materials may also advantageously be impregnated with one and/or rubber. Fibrous materials may also advantageously be impregnated with one	40
40	and/or rubber. Fibrous materials may also advantageously or soaps and detergents or more compounds of the present invention. For example, some soaps and detergents or more compounds of the present invention, relative to those of the compounds of	•••
40	or more compounds of the present invention. For example, some steps of the compounds of possess a bactericidal action, but such action, relative to those of the compounds of possess a bactericidal action, but such action, relative to those of the compounds of possess a bactericidal action, but such and of little effect in comparison with the overall	
	possess a bactericidal action, but such action, relative to thick the overall the present invention, is weak and of little effect in comparison with the overall the present invention, is weak and of little effect in compositions, the compounds of the	
	the present invention, is weak and of firme enert in tunipations, the compounds of the germicidal activity of the composition. In such compositions, the compounds of the germicidal activity of the composition concentrations as low as 10 p.p.m., although,	
	germicidal activity of the composition. In such composition, as 10 p.p.m., although, present invention may be employed in concentrations as low as 10 p.p.m. or 0.001%	45
	present invention may be employed in concentrations as much as 50 p.p.m. or 0.001% from a practical point of view, it is desirable to use as much as 50 p.p.m. or 0.001% from a practical point of view, it is desirable to use as much as 10% or 5%, or even more.	45
45	from a practical point of view, it is desirable to the last of 5%, or even more, by weight, or 0.01%, 0.1%, 0.5% or as much as 1% or 5%, or even more, by weight, or 0.01%, 0.1%, or even more, of the present invention are those comprising	
	by weight, or 0.01%, 0.1%, 0.5% or as much as 1% to represent invention are those comprising Particularly useful compositions of the present invention are those comprising	
	Particularly useful compositions of the present inventic detergents in which the soaps and detergents, and especially toilet soaps of cosmetic detergents in which the soaps and detergents, and especially toilet soaps of cosmetic participants of 0.01%,	
	soaps and detergents, and especially toilet soaps of content to the present invention may be employed in concentrations of 0.01%, compounds of the present invention may be employed.	
	compounds of the present invention may be employed in tracentrations of compounds of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention may be employed in tracentrations of the present invention in t	50
50	0.1%, 0.5% or even up to 11% by weight, or more. The term of the compositions, including herein will be used to include all synthetic and natural cleansing compositions, including herein will be used to include all synthetic and natural cleansing compositions, including herein will be used to include all synthetic and natural cleansing compositions, including herein will be used to include all synthetic and natural cleansing compositions, including herein will be used to include all synthetic and natural cleansing compositions.	
	herein will be used to include all synthetic and natural creatising compositions, herein will be used to include all synthetic and natural creatising compositions, such as dimethyl stearamido-propyl-2-hydroxy-ammonium cationic detergents, such as commercial soaps, e.g., alkali metal	
	cationic detergents, such as dimetryl stegrammo-property and similar acids, e.g., alkali metal dihydrogen phosphate, anionic detergents, such as commercial soaps, e.g., alkali metal dihydrogen phosphate, anionic detergents, such as commercial soaps, e.g., alkali metal	
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	scaps of hydrolyzed natural or syndlettic detergents, such as sarcosine,	55
55	endium and Dollassium steatures of the control of t	
	non-ionic detergents, such as paryonappropriate propriet thereof. The term	
•	detergents, such as starcies, vegetable builty meaning i.e. a cleansing	
	detergents, such as starches, vegetable gums, and the introduction detergents, such as starches, vegetable gums, and the introduction meaning, i.e., a cleansing "soap" employed herein is used in its popular or ordinary meaning, i.e., a cleansing "soap" employed herein is used in its popular or ordinary meaning, i.e., a cleansing	
	composition prepared from an alkan metal and amortised	60
60	hydroxide and a fat of fatty acid, both saturation is the use thereof	
w	Another valuable use of the compounds of Learning tentiles and paper pulp,	
	Another valuable use of the compounds of the present invention in the paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, textiles, and paper pulp, to sanitize fibrous material, such as cotton gauze, dressings, and the sanitize fibrous fibrou	
	to sanitize fibrous material, such as cotton gauze, uresnings, terms, They also serve as preferably in concentrations of about 0.01% to 0.5% by weight. They also serve as preferably in concentrations of about 0.01% to 0.5% by weight. They also serve as	
	preferably in concentrations of about 0.01% to 0.5% by weight 1167 and prior to antiseptic agents, when incorporated in plastic or rubber compositions, prior to	
	annishes some	

molding into articles of commerce, such as baby rattles, gloves, and food wrappers, preferably in concennations of 0.0051% to 0.51% by weight.

TABLE II

Compound 3-Phenylbenzonszine-2,4-dione 6,8-Dibromo-3(3-triffnoromethylphenyl)-1,3-benzozazi 3-(3-Triffuoromethylphenyl)-1,3-benzozazine 3-(3-Triffuoromethyl-2-chloro-phenyl)-1,3-benzozazine	Effectiveness Against S. aurens MIC × 10*	1:1 — 1:10	ne-2,4-dione 1:1000 1:10,000	1:100 — 1:1000	-2,4-dione 1:10.000 - 1:10.000
	Compound	3-Phenylbenzonazine-2,4-dione	6,8-Dibromo-3(3-triffnoromethylphenyl)-1,3-benzoxazine-2,4-dione	3-(3-Triffuoromethylphenyl)-1,3-benzoxazine-2,4-dione	3-(3-Trifluaromethyl-2-chloro-phenyl)-1,3-benzoxazine-2,4-dione

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WHAT WE CLAIM IS:—
1. Compounds having the general formula:

$$x_n - x_n = 0$$

	2	_
5 .	Where: X and X ¹ are chlorine, bromine, iodine, or CF ₃	5
) .	is an integer from 0 to 3, subject to the proviso that A of 12 Appears	
	least one and not more than two CF _s groups,	
	Y is sulphur or oxygen, and	•
	7 is subshape on costron	10
10		
	3. Compounds according to claim 1, wherein 1 is oxygen and 2 is	
	- Lamin - is an integer from 1 to 1.	
	4. Compounds according to claim 1 wherein Y is sulphur and wherein n is an 5. Compounds according to claim 1 wherein Y is sulphur and wherein n is an	15
15	6. Compounds according to claim 1 wherein Y is oxygen, Z is sulphur and	
	6. Compounds according to claim I whatche I be only	
	wherein n is an integer from 1 to 3. 7. The compound 3-(3-trifluoromethylphenyl)-1,3-benzoxazine-2,4-dione.	
	7. The compound 3-(3-trifluoromethylphenyl)-1,3-benzoxazine-2,4-8. The compound 6,8-dibromo-3-(3-trifluoromethylphenyl)-1,3-benzoxazine-2,4-	20
	8, The compound byo-designs (20
20	dione. 9. The compound 6,8-dibromo-3-(1,3-dichloro-4-trifluoromethylphenyl)-1,3-	
	A A Million	
	10 Compositions comprising at least one compound according	
	preceding claims, together with an inert pharmaceutical diluent.	25
25		
2	11. Compositions comprising at test one compound according to any of claims	
	12 Compositions comprising at least one composite assets	
	1 to 9 together with plastics and/or rubbet. 13. Fibrous materials whenever impregnated with at least one compound accord-	30
30	ing to any of claims 1 to 9. 14. Compositions according to claim 11 wherein the total weight of said com-	
	14. Compositions according to that wherein the composition. pounds is in the range 0.001% to 5% of the total weight of the composition.	
	pounds is in the range 0.001% to 5% of the total weight of said com- 15. Compositions according to claim 12 wherein the total weight of said com-	
	15. Compositions according to claim 12 which might of the composition. pounds is in the range 0.005% to 0.5% of the total weight of the composition.	35
	pounds is in the range 0.005% to 0.5% of the total weight of said 16. Fibrous materials according to claim 13 wherein the total weight of said impregnated	22
35	16. Fibrous materials according to claim 15 whether weight of said impregnated compounds is in the range 0.01% to 0.5% of the total weight of said impregnated	
	iala	
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Learnington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.

—1968. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.